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**COMMENTS:**

**U.S. S.N. 09/905,235**  
**Our docket: LA24B Cont1**

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BY FACSIMILE

CASE LA24BCont1 NP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
IN RE APPLICATION OF

Robl et al.

Examiner: Abdel A. Mohamed

APPLICATION NO: 09/905,235

Rt Unit: 1653

FILED: July 13, 2001

FOR: METHOD FOR TREATING ATHEROSCLEROSIS EMPLOYING  
AN  $\alpha$ P2 INHIBITOR AND COMBINATION

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OCT 24 2003

Assistant Commissioner for Patents  
Washington, D.C. 20231

RESPONSE TO RESTRICTION REQUIREMENT

OFFICIAL

Sir or Ma'am:

In response to the restriction requirement dated September 24, 2003 having a shortened statutory period for reply due on October 24, 2003, please enter the following amendments and consider the remarks below. "Amendments to the Claims" begins on page 2 of this response and the "Remarks" begin on page 19. A copy of the provisional election (and postcard) mailed August 8 beings on page 20.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Original): A method for treating atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of an aP2 inhibitor.
2. (Original): The method as defined in Claim 1 wherein the aP2 inhibitor binds to the aP2 protein and inhibits its function and/or its ability to bind free fatty acids.
3. (Previously Amended): The method as defined in Claim 1 wherein the aP2 inhibitor contains a hydrogen bond donator or acceptor group and interacts directly or through an intervening water molecule either by ionic or hydrogen bonding interactions, with one, two, or three of the three amino acid residues, designated as Arg 106, Arg 126 and Tyr 128 in human aP2 within the aP2 protein (SEQ ID NO:1).
4. (Original): The method as defined in Claim 3 wherein the hydrogen bond donator or acceptor group is acid in nature.
5. (Original): The method as defined in Claim 3 where said aP2 inhibitor contains an additional substituent which binds to  
20 (in) and/or interacts with a discrete pocket within the aP2 protein defined roughly by the amino acid residues Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2.
6. (Original): The method as defined in Claim 5 wherein said  
25 additional substituent in said aP2 inhibitor is hydrophobic in nature.
7. (Original): The method as defined in Claim 5 in which the  
through space distance from the hydrogen bond donor/acceptor group and the additional substituent group  
30 in said aP2 inhibitor is within the distance of about 7 to about 15 Angstroms.
8. (Original): The method as defined in Claim 1 wherein Type II diabetes is treated.

9. (Original): The method as defined in Claim 1 wherein the aP2 inhibitor is employed in the form of a pharmaceutically acceptable salt thereof or a prodrug ester thereof.

10. (Original): The method as defined in Claim 1 wherein the aP2 inhibitor includes an oxazole or analogous ring, a pyrimidine derivative or a pyridazinone derivative.

11. (Original): The method as defined in Claim 10 wherein the aP2 inhibitor is a substituted benzoyl or biphenyl-2-oxazole-alkanoic acid derivative, an oxazole derivative, a 2-thio-4,5-diphenyloxazole S-derivative, a phenyl-heterocyclic oxazole derivative, a diaryloxazole derivative, a 4,5-diphenyloxazole derivative, an oxazole carboxylic acid derivative, a phenyloxazolyloxazole derivative, or a 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acid derivative.

12. (Original): The method as defined in Claim 10 wherein the aP2 inhibitor is a 2-benzoyloxypyrimidine derivative, a dihydro(alkylthio)(naphthylmethyl)oxy pyrimidine derivative, a thiouracil derivative, or an  $\alpha$ -substituted pyrimidine-thioalkyl or alkyl ether derivative.

13. (Original): The method as defined in Claim 10 wherein the aP2 inhibitor is a pyridazinone acetic acid derivative.

14. (Currently Amended): The method as defined in Claim 10 wherein the aP2 inhibitor is

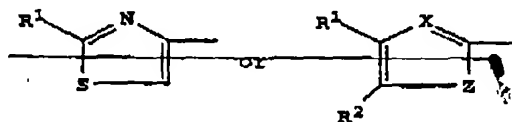
25 ~~(i) a substituted benzoylbenzene or biphenyl-alkanoic acid derivative having the structure:~~



wherein

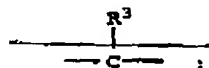
~~A is a group having the formula~~

30

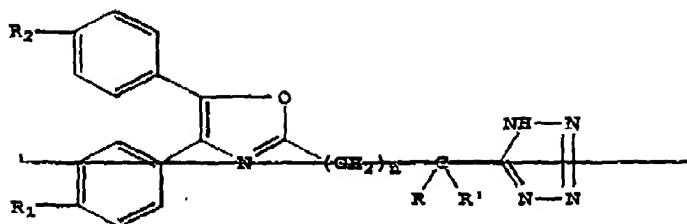


wherein

~~X is N or~~



II



in which,

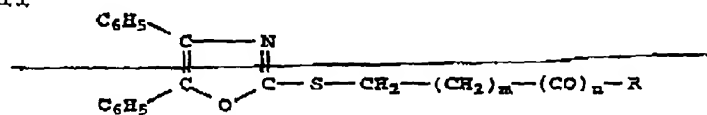
~~R and R' are identical or different and represent a~~  
 5 ~~hydrogen atom or an alkyl radical containing 1 or 2 carbon~~  
~~atoms,~~

~~R<sub>1</sub> and R<sub>2</sub> are identical or different and represent~~  
~~hydrogen or halogen atoms or alkyloxy radicals in which the~~  
~~alkyl portion contains 1 to 4 carbon atoms in a straight or~~  
 10 ~~branched chain, and~~

~~n equals 3 to 6, as well to their salts;~~

~~(III) 2-thiol-4,5-diphenyloxazole S derivatives~~  
 which have the structure

III



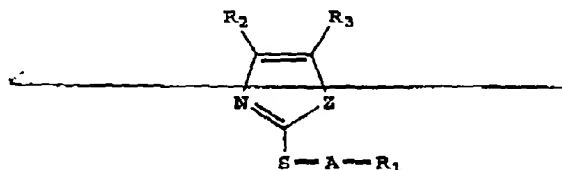
15

wherein m is 0, 1 or 2, n is 1 and R represents hydroxy,  
 alkoxy or amino, and pharmaceutically acceptable addition  
 salts thereof;

~~(IV)azole derivatives of the structure~~

20

IV



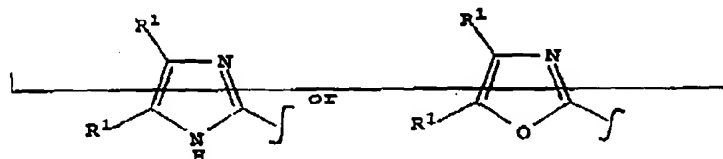
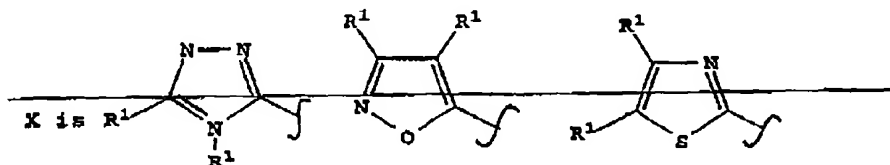
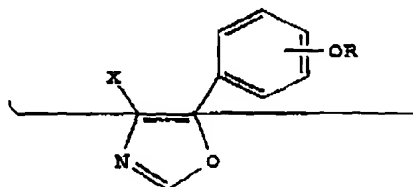
25

wherein R<sub>1</sub> is carboxyl, esterified carboxyl or other  
 functionally modified carboxyl group; R<sub>2</sub> and R<sub>3</sub> each are  
 aryl of up to 10 carbon atoms; A is C<sub>n</sub>H<sub>2n</sub> in which n is an  
 integer from 1 to 10, inclusive; and Z is O or S, and  
 physiologically acceptable salts thereof;

4

~~(V) phenyl-heterocyclic oxazole derivatives which have the structure~~

~~V~~

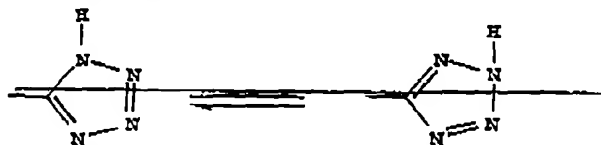


5

~~R is  $\text{CH}_2\text{R}^2$ ;~~

~~$\text{R}^1$  is Ph or Th;~~

~~$\text{R}^2$  is~~



~~$\text{CO}_2\text{R}^1$ , and~~

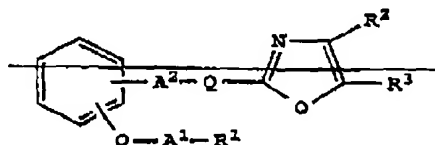
10

~~$\text{R}^2$  is H, or  $\text{C}_1$   $\text{C}_4$  lower alkyl,~~

~~or pharmaceutically acceptable salt thereof;~~

~~(VI) diaryloxazole derivatives having the structure~~

~~VI~~



15 ~~wherein  $\text{R}^1$  is carboxy or protected carboxy,~~

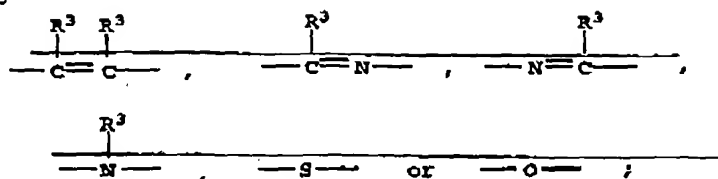
~~$\text{R}^2$  is aryl,~~

~~$\text{R}^3$  is aryl,~~

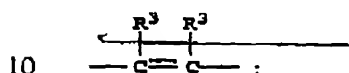
~~$\text{R}^1$  is lower alkylene.~~

5

Z is



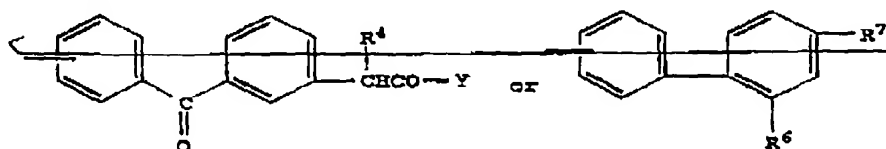
- 5 ~~R<sup>1</sup> is hydrogen, lower alkyl or phenyl;~~  
~~R<sup>2</sup> is hydrogen or lower alkyl, or~~  
~~R<sup>1</sup> and R<sup>2</sup> taken together form a benzene ring, with~~  
~~the proviso that when X is N, Z is other than~~



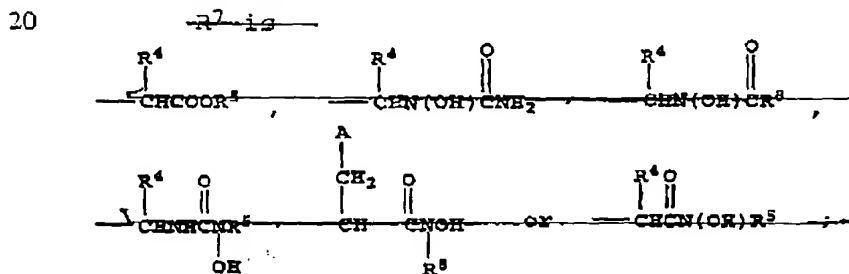
~~R<sup>3</sup> is hydrogen or lower alkyl;~~

~~n is 1-3;~~

~~B is~~



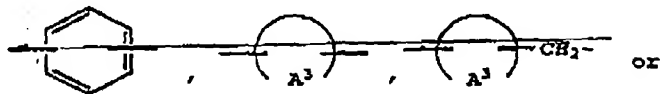
- 15 ~~wherein~~  
~~Y is OR<sup>5</sup> or N(OH)R<sup>8</sup>;~~  
~~R<sup>4</sup> and R<sup>5</sup> are each, independently, hydrogen or lower~~  
~~alkyl;~~  
~~R<sup>6</sup> is hydrogen, halo or nitro;~~  
~~R<sup>7</sup> is~~



- ~~R<sup>8</sup> is lower alkyl;~~  
~~m is 0-3;~~  
 25 ~~or a pharmacologically acceptable salts thereof;~~  
 (II) ~~oxazole derivatives which have the structure~~

~~A<sup>2</sup> is bond or lower alkylene and~~

~~Q is~~



~~(in which  $A^3$  is cyclo (lower) alkane or~~

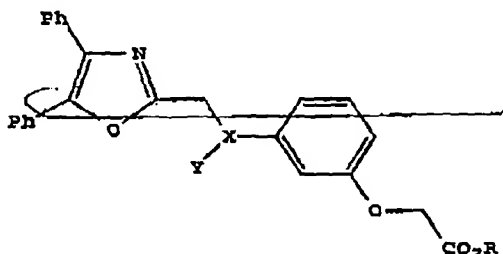
~~cyclo (lower) alkane,~~

~~each of which may have suitable substituent(s));~~

~~(VII) 4,5-diphenyloxazole derivatives having the~~

~~structure~~

~~VIIA~~



10

~~wherein~~

~~R is H or  $C_1$ - $C_5$  lower alkyl,~~

~~X is N or  $CH_2$ ,~~

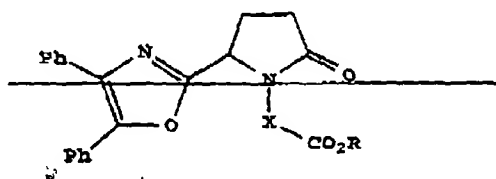
~~Y is H or  $CO_2R^1$ , or  $COR^2$ , provided that when X is  $CH_2$ ,~~

15 ~~Y is not H,~~

~~$R^1$  is  $C_1$ - $C_5$  lower alkyl, or phenylmethyl, and~~

~~$R^2$  is  $C_1$ - $C_5$  alkyl,~~

~~VIIIB~~



20 ~~wherein~~

~~R is H or  $C_1$ - $C_5$  lower alkyl,~~



~~X is  $(CH_2)_n$  or para or meta substituted phenyl~~

~~wherein the substituent is  $OR^2$ ,~~

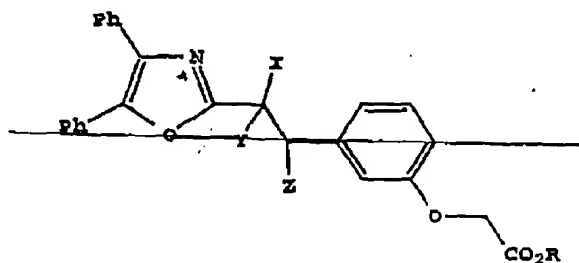
~~$R^2$  is  $C_1-C_5$  alkyl, and~~

~~n is an integer of 4 to 8,~~

5 ~~and pharmaceutically acceptable salts thereof,~~

~~(VIII) oxazole carboxylic acid derivatives having the structure~~

~~VIII~~



10

~~wherein~~

~~Y and Z are independently hydrogen or together form a bond,~~

~~X is CN,  $CO_2R^1$  or  $CONR^2R^3$ ,~~

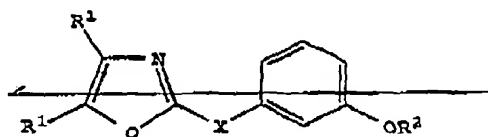
15 ~~R and  $R^1$  are independently or together H, Na, or  $C_1-C_5$  lower alkyl,~~

~~$R^2$  and  $R^3$  are independently or together H, or  $C_1-C_5$  lower alkyl,~~

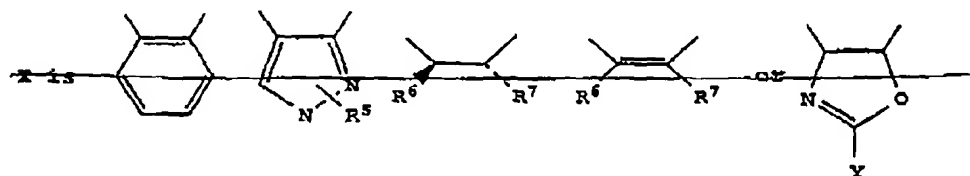
~~or alkali metal salt thereof,~~

20 ~~(IX) phenyloxazolyloxazole derivatives having the structure~~

~~IX~~



~~wherein:~~



25

~~Y is CH<sub>3</sub>, Ph, or OH, provided that when Y is OH, the compound exists in the keto-enol tautomerism form~~



~~R<sup>1</sup> is Ph or Th,~~

~~R<sup>2</sup> is CH<sub>2</sub>R<sup>3</sup>,~~

~~R<sup>3</sup> is CO<sub>2</sub>R<sup>4</sup>,~~

~~R<sup>4</sup> is H or C<sub>1</sub>-C<sub>5</sub> lower alkyl,~~

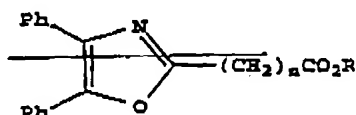
~~R<sup>5</sup> is H or CH<sub>3</sub>; R<sup>6</sup> is OHCN or H<sub>2</sub>N; and~~

~~R<sup>7</sup> is H or OH,~~

10 or pharmaceutically acceptable salt thereof,

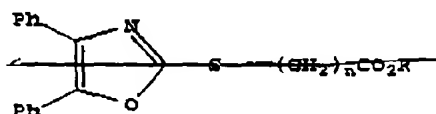
~~(X) 2-(4,5-diaryl)-2-oxazolidinone substituted  
phenylalkanoic acids and esters having the structure~~

~~XA—~~



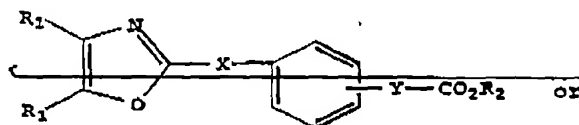
15

~~XB—~~



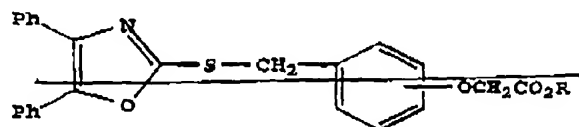
~~(wherein n is 7-9 and R is hydrogen or lower alkyl; or when  
R is hydrogen, the alkali metal salt thereof),~~

~~XC—~~



20

~~XD—~~



~~wherein~~

~~R<sub>1</sub> is phenyl or thienyl;~~

~~$R_2$  is hydrogen, lower alkyl or together with  $CO_2$  is tetrazol-1-yl;~~

~~X is a divalent connecting group selected from the group consisting of  $CH_2CH_2$ ,  $CH=CH$ , and  $CH_2O$ ;~~

5 ~~Y is a divalent connecting group attached to the 3 or 4-phenyl position selected from the group consisting of  $OCH_2$ ,  $CH_2CH_2$  and  $CH=CH$ ,~~

~~or when  $R_2$  is hydrogen, an alkali metal salt thereof;~~

10 ~~(XI) substituted 4,5 diaryl heterocycles having the formula~~

~~XI~~



~~in which~~

15 ~~each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;~~

~~X is nitrogen or CR<sup>1</sup>;~~

~~Y is nitrogen,  $N(CH_2)_nA$  or  $C(CH_2)_nA$ ;~~

20 ~~Z is nitrogen, oxygen or  $N(CH_2)_nA$ , and the dotted line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;~~

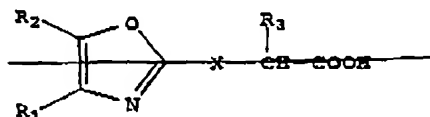
~~$R^1$  is hydrogen,  $C_{1-4}$ alkyl, optionally substituted phenyl or optionally substituted heteroaryl;~~

~~n is 4 to 12; and~~

25 ~~A is  $CO_2H$  or a group hydrolysable to  $CO_2H$ , 5-tetrazolyl,  $SO_3H$ ,  $P(O)(OR)_2$ ,  $P(O)(OH)_2$ , or  $P(O)(R)(OR)$  in which R is hydrogen or  $C_{1-4}$ alkyl, or a pharmaceutically acceptable salt thereof;~~

~~(XII) compounds which have the structure~~

30 ~~XII~~



~~where X is O or S;~~

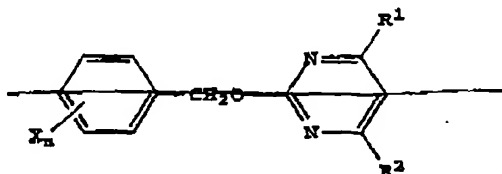
~~R<sub>1</sub> is H, phenyl or phenyl substituted with F, Cl or Br or alkoxy,~~

~~R<sub>2</sub> is H, alkyl, phenyl or phenyl substituted with F, Cl or Br or alkoxy, and~~

5 ~~R<sub>3</sub> is H or alkyl,~~

~~(XIII) 2-benzoyloxy-pyrimidine derivatives having the following structure~~

~~XIII~~



10 ~~wherein~~

~~R<sup>1</sup> and R<sup>2</sup> are each independently H, a halogen, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>3</sub>-C<sub>5</sub> alkenyl, C<sub>3</sub>-C<sub>5</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, C<sub>3</sub>-C<sub>5</sub> alkenyloxy, C<sub>3</sub>-C<sub>5</sub> alkynyloxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, or phenyl, with the~~

15 ~~proviso that at least one of R<sup>1</sup> and R<sup>2</sup> must be hydroxyl,~~

~~n is an integer of 0 to 5, and~~

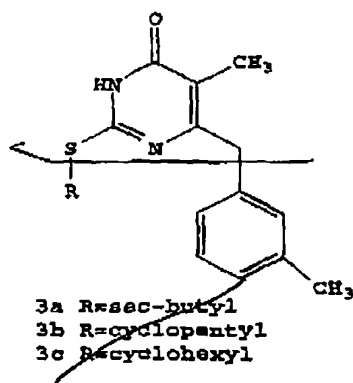
~~each X which may be identical or different if n is greater than 1, is a halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>3</sub>-C<sub>5</sub> aralkyloxy, phenyl,~~

20 ~~hydroxymethyl, hydroxycarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxy-carbonyl, or nitro,~~

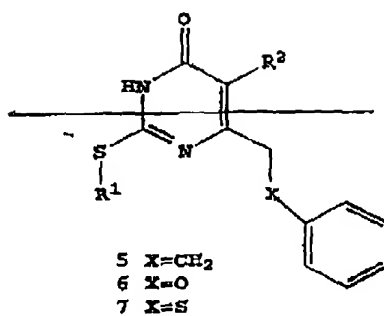
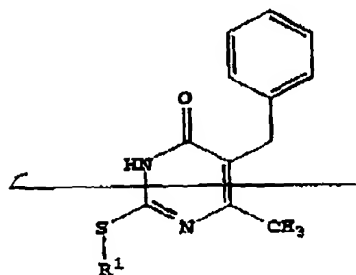
~~(XIV) dihydro(alkylthio)(naphthylmethyl)~~

~~oxypyrimidines which have the structures~~

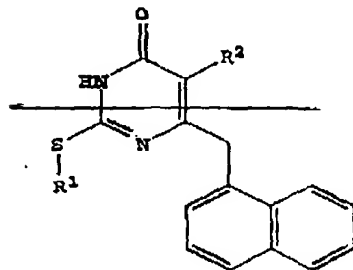
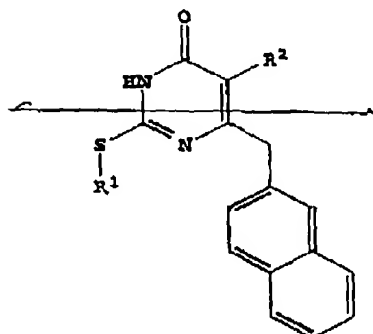
XIVA



25

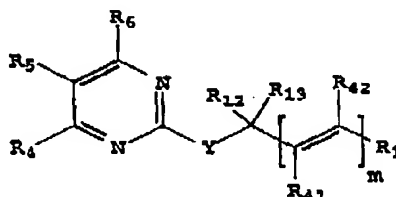
~~XIVB~~~~XIVC~~

5

~~XIVD~~~~XIVE~~

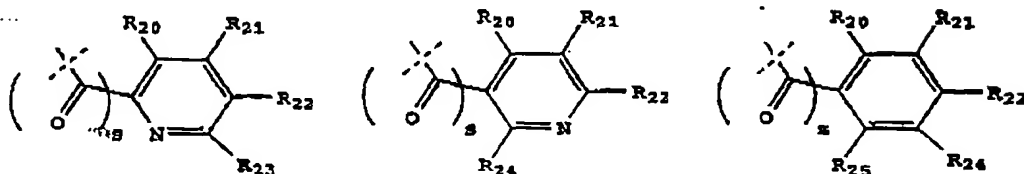
10  ~~$R^1$  = sec-butyl, cyclopentyl, cyclohexyl;~~  
 ~~$R^2$  = H,  $CH_3$ , including tautomers of the above;~~

~~(XVI)~~  $\alpha$ -substituted pyrimidine-thioalkyl and  
alkylether compounds which have the structure  
XVI



5 where m is 0 or 1;

R<sup>1</sup> is selected from -CO<sub>2</sub>R<sub>53</sub>, -CONR<sub>54</sub>R<sub>55</sub>,



- 10 where s is 0 or 1, and R<sub>20</sub>, R<sub>21</sub>, R<sub>22</sub>, R<sub>23</sub>, R<sub>24</sub>, and R<sub>25</sub> are  
the same or different and are selected from -H, C<sub>1</sub>-C<sub>6</sub>  
alkyl, C<sub>1</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>3</sub>-C<sub>8</sub>  
cycloalkyl, -CF<sub>3</sub>, -NO<sub>2</sub>, -halo, -OH, -CN, phenyl,  
phenylthio, -styryl, -CO<sub>2</sub>(R<sub>31</sub>), -CON(R<sub>31</sub>)(R<sub>32</sub>), -CO(R<sub>31</sub>), -  
15 (CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>), -C(OH)(R<sub>31</sub>)(R<sub>33</sub>), -(CH<sub>2</sub>)<sub>n</sub>N(R<sub>31</sub>)(CO(R<sub>33</sub>)),  
(CH<sub>2</sub>)<sub>n</sub>N(R<sub>31</sub>)(SO<sub>2</sub>(R<sub>33</sub>)), or where R<sub>20</sub> and R<sub>21</sub>, or R<sub>21</sub> and R<sub>22</sub>,  
or R<sub>22</sub> and R<sub>23</sub> are taken together to form a five or six-  
membered saturated or unsaturated ring containing 0 or 1  
oxygen, nitrogen or sulfur, where the unsaturated ring may  
be optionally substituted with 1, 2 or 3, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-  
20 C<sub>6</sub> alkoxy, -OH, -CH<sub>2</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>), -C<sub>3</sub>-C<sub>8</sub>  
cycloalkyl, -CF<sub>3</sub>, -halo, CO<sub>2</sub>(R<sub>31</sub>), -CON(R<sub>31</sub>)(R<sub>32</sub>), -CO(R<sub>31</sub>),  
-(CH<sub>2</sub>)<sub>n</sub>N(R<sub>31</sub>)(CO(R<sub>33</sub>)), -(CH<sub>2</sub>)<sub>n</sub>N(R<sub>31</sub>)(SO<sub>2</sub>(R<sub>33</sub>)), -CN, -CH<sub>2</sub>CF<sub>3</sub>  
or -CH(CF<sub>3</sub>)<sub>2</sub>, or phenyl and the saturated ring may be  
optionally substituted with 1, 2 or 3, -C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>1</sub>-C<sub>6</sub>  
25 alkoxy, -OH, -CH<sub>2</sub>OH or -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>) or one oxo (=O);  
where n is 0-3 and R<sub>31</sub>, R<sub>32</sub> and R<sub>33</sub> are the same or  
different and are selected from

-H,  
C<sub>1</sub>-C<sub>6</sub> alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, -OH or -CN,

or where R<sub>31</sub> and R<sub>32</sub> taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C<sub>1</sub>-C<sub>6</sub>alkyl)piperazinyl, or a member selected from

1-cyclohexenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-imidazolyl, 4-imidazolyl, 2-benzothiazolyl, 2-benzoxazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 5-methyl-3-isoxazolyl, 5-phenyl-3-isoxazolyl, 4-thiazolyl, 3-methyl-2-pyrazinyl, 5-methyl-2-pyrazinyl, 6-methyl-2-pyrazinyl, 5-chloro-2-thienyl, 3-furyl, benzofuran-2-yl, benzothien-2-yl, 2H-1-benzopyran-3-yl, 2,3-dihydrobenzopyran-5-yl, 1-methylimidazol-2-yl, quinoxalin-2-yl, piperon-5-yl, 4,7-dichlorobenzoxazol-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, 2,4-dimethylpyrimidin-6-yl, 2-methylpyrimidin-4-yl, 4-methylpyrimidin-6-yl, 6-chloropiperon-5-yl, 5-chloroimidazol[1,2-a]pyridin-2-yl, 1-H-inden-3-yl, 1-H-2-methyl-inden-2-yl, 3,4-dihydronaphth-1-yl, S-4-isopropenylcyclohexen-1-yl or 4-dihydronaphth-2-yl; where R<sub>53</sub> is selected from -H, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, phenyl (optionally substituted with 1, 2, or 3 -halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, -OH, -CN), or a five or six-membered unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with -H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -OH, -CH<sub>2</sub>OH, or -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>);

where R<sub>54</sub> and R<sub>55</sub> being the same or different are selected from -H, C<sub>1</sub>-C<sub>6</sub> alkyl, allyl, or phenyl (optionally substituted with 1, 2 or 3 -halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy or -CF<sub>3</sub>), or taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C<sub>1</sub>-C<sub>6</sub>alkyl)piperazinyl;

R<sub>41</sub> and R<sub>42</sub>, being the same or different, are selected from -H and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>12</sub> is selected from -H, C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -CN, -C(O)NH<sub>2</sub>, -C(O)N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl), -  
5 CO<sub>2</sub>H, -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -CH<sub>2</sub>OH, -CH<sub>2</sub>NH<sub>2</sub> or -CF<sub>3</sub>;

R<sub>13</sub> is selected from -H, C<sub>1</sub>-C<sub>6</sub> alkyl or -CF<sub>3</sub>;

Y is selected from -S-, -S(O)-, -S(O)<sub>2</sub>, or -O-;

R<sub>4</sub> is -OH;

R<sub>5</sub> is selected -H, -C<sub>2</sub>H<sub>4</sub>OH, -C<sub>2</sub>H<sub>4</sub>-O-TBDMS, halo, -C<sub>3</sub>-  
10 C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, -CH<sub>2</sub>CH<sub>2</sub>Cl or C<sub>1</sub>-C<sub>4</sub> alkyl, with the proviso that R<sub>5</sub> is not isobutyl;

or, when R<sub>6</sub> is hydroxyl, R<sub>4</sub> and R<sub>5</sub> are taken together to form a five or six-membered saturated or unsaturated ring which together with the pyrimidine ring form the group  
15 consisting of 7H-pyrrolo[2,3-d]pyrimidine, 5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidine, furo[2,3-d]pyrimidine, 5,6-dihydro-furo[2,3-d]pyrimidine, thieno[2,3-d]pyrimidine, 5,6-dihydro-thieno[2,3-d]pyrimidine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-purine, pyrimido[4,5-d]pyrimidine,  
20 pteridine, pyrido[2,3-d]pyrimidine, or quinazoline, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C<sub>1</sub>-C<sub>6</sub> alkyl C<sub>1</sub>-C<sub>6</sub> alkoxy, -OH, -CH<sub>2</sub>OH, or -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>), -C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -CF<sub>3</sub>, -halo, -CO<sub>2</sub>(R<sub>31</sub>), -CON(R<sub>31</sub>)(R<sub>32</sub>), -CO(R<sub>31</sub>), -(CH<sub>2</sub>)<sub>n</sub>N(R<sub>31</sub>)(CO(R<sub>33</sub>)), -  
25 (CH<sub>2</sub>)<sub>n</sub>N(R<sub>31</sub>)(SO<sub>2</sub>(R<sub>33</sub>)), and the saturated ring may be optionally substituted with 1, 2 or 3, -C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -OH, -CH<sub>2</sub>OH, or -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>) or one oxo (=O); and

R<sub>6</sub> is selected from -H, -OH, halo, -CN, -CF<sub>3</sub>, -  
30 CO<sub>2</sub>(R<sub>61</sub>), -C(O)R<sub>61</sub> or -C(O)N(R<sub>61</sub>)(R<sub>62</sub>) where R<sub>61</sub> and R<sub>62</sub> are the same or different and are selected from

-H,

C<sub>1</sub>-C<sub>6</sub> alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo,  
35 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, -OH, -CN,

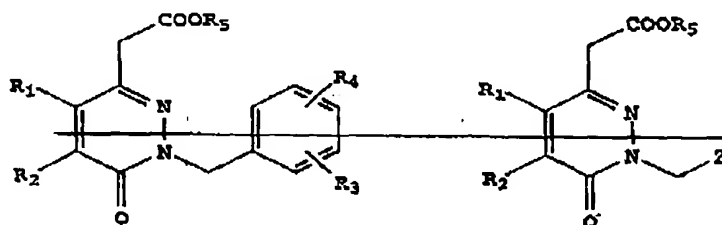
or where R<sub>61</sub> and R<sub>62</sub> taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -



piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, or -4-(C<sub>1</sub>-C<sub>6</sub> alkyl)piperazinyl;

pharmaceutically acceptable salts, hydrates, N-oxides and solvates thereof].

5 ~~(XVII) compounds which have the structure~~



XVII

10 where R<sub>1</sub> and R<sub>2</sub> are H, alkyl, aryl or arylalkyl, where the alkyl can include as substituents halogen, CF<sub>3</sub>, CH<sub>3</sub>O, CH<sub>3</sub>S, NO<sub>2</sub>, or R<sub>1</sub> and R<sub>2</sub> with the carbons to which they are attached can form methylenedioxy, or

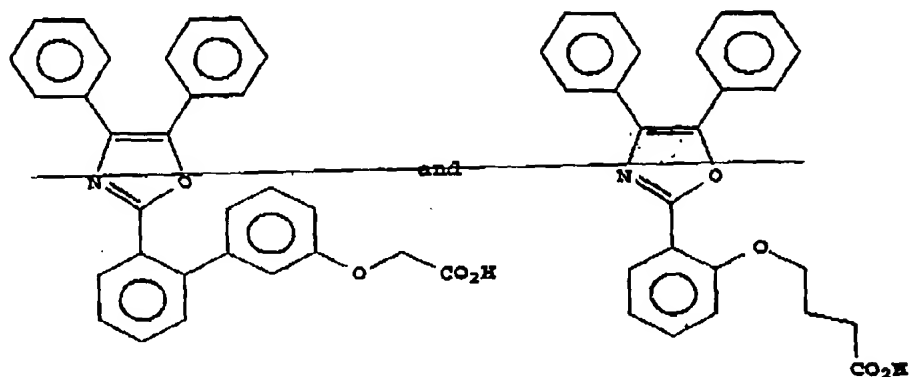
~~R<sub>1</sub> and R<sub>2</sub> can form a C<sub>5</sub>-C<sub>7</sub> non-aromatic ring, or a heterocycle which can be pyridine, pyrazine, pyrimidine, pyridazine, indol, or pyrazole, or an oxygen containing heterocycle which can be pyran or furan, or a sulfur containing heterocycle which can be thiopyran, or thiophene, the heterocycles being optionally substituted with halogen or alkyl.~~

~~R<sub>3</sub> and R<sub>4</sub> are H, alkyl, halogen, CF<sub>3</sub>, CH<sub>3</sub>O, CH<sub>3</sub>S or~~  
20 ~~NO<sub>2</sub> or R<sub>3</sub> and R<sub>4</sub> with the carbons to which they are~~  
~~attached can form a methylenedioxy group;~~

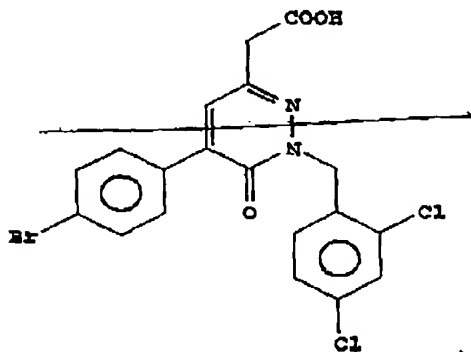
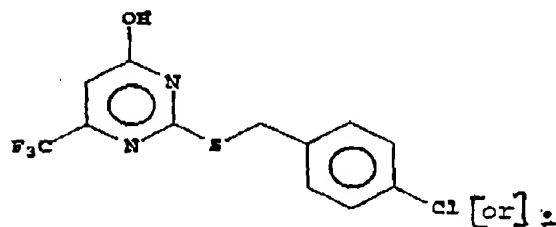
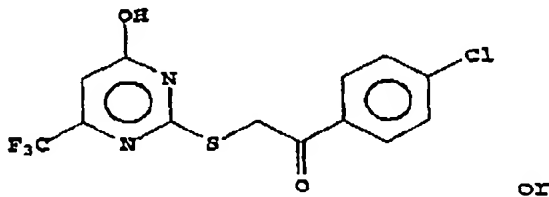
~~R<sub>5</sub> is II, and~~

~~2~~ is a heterocycle which can be pyridine, thiazole, benzothiazole, benzimidazole or quinoline, which 2 group  
25 ~~can optionally be substituted with halogen or alkyl.~~

15. (Currently Amended) The method as defined in Claim 1 wherein the aP2 inhibitor has the structure



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LA24'b

16. (Withdrawn): A pharmaceutical combination comprising an ap2 inhibitor and another type antiatherosclerotic agent.

17. (Withdrawn): The combination as defined in Claim 16 wherein the other antiatherosclerotic agent is an MTP inhibitor, an  
5 HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, other cholesterol lowering agent, a lipoxxygenase inhibitor, an ACAT inhibitor or a PPAR  $\alpha/\gamma$  dual agonist.

18. (Withdrawn): The combination as defined in Claim 16 wherein  
10 the antiatherosclerotic agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin or fluvastatin.

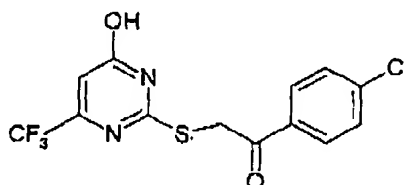
19. (Withdrawn): The combination as defined in Claim 16 wherein the ap2 inhibitor is present in a weight ratio to the  
15 antiatherosclerotic agent within the range from about 0.01 to about 100:1.

20. (Withdrawn): A method for treating atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a  
20 pharmaceutical combination as defined in Claim 16.

**REMARKS**

The Examiner alleges that the claims of this application recite 2 separate classes of invention which are related by combination (Group II – claims 1-15) and subcombination (I – claims 16-20) and requires that the Applicant elect one of these classes for prosecution. The Examiner further Applicants to Election a species from restriction/elections requirements previously entered in the parent application, U.s. Serial No. 09/390,275.

Applicants have already chosen a group and species in a provisional election mailed August 8, 2001. A copy of this election and postcard are included at the end of this amendment. In brief, the election was worded as follows: "Based on the Restriction/Election requirements previously entered in the parent application U.S. Serial No. 09/390,275, Applicants herein provisionally elect to prosecute the invention of Group I (claims 1-15), and further elect the species of Group XVI, with the ultimate specie being:



Applicants submit that Claims 1-10, 12, 14 and 15 read on the elected species." This election is herein re-affirmed and Applicants request that the Examiner act on this election.


Applicants also traverse the restriction requirement for the following reason. Groups I and II would not require multiple searches, but only a search on an aP2 inhibitor, the concept common to both the method and pharmaceutical compositions of Groups I and 2. Accordingly, a search on all the claims would not be unduly burdensome. MPEP § 803.01 addresses this situation as follows:

**[If] the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.**

Accordingly, Applicants believe the entire application should be searched.

Respectfully submitted,

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609-252-5323  
Date: October 24, 2003

  
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CASE LA 24B Cont1

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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Ronald S. Hermenau  
Type or print name

*Ronald S. Hermenau*  
Signature

August 8, 2001  
Date

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ROBL ET AL

Examiner: Not Assigned Yet

APPLICATION NO: 09/905,235

FILED: JULY 13, 2001

FOR: METHOD FOR TREATING ATHEROSCLEROSIS EMPLOYING AN  
AP2 INHIBITOR AND COMBINATIONRECEIVED  
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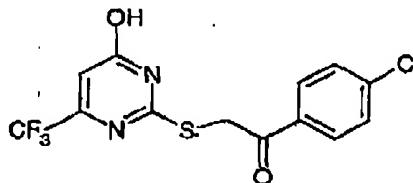
OCT 24 2003

OFFICIAL

Assistant Commissioner for Patents  
Washington, D.C. 20231PROVISIONAL ELECTION OF SPECIES

Sir:

Based on the Restriction/Election requirements previously entered in the parent application U.S. Serial No. 09/390,275, Applicants herein provisionally elect to prosecute the invention of Group I (claims 1-15), and further elect the species of Group XVI, with the ultimate specie being:



Applicants submit that Claims 1-10, 12, 14 and 15 read on the elected species.

Respectfully submitted,

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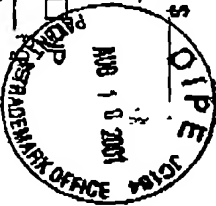
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Case No.: LA 248 Cont. 1Application No.: 09/905,235Mailing Date: August 8, 2001Due Date: N/A

Express Mail No.: \_\_\_\_\_

The Patent &amp; Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below:

☐ Amendment/Response/Letter - Fee \$ 01PE  
☐ Appin. Filing Papers - Fee \$ \_\_\_\_\_  
☐ Non-provisional  
☐ Provisional Application  
☐ CPA ☐ DIV ☐ CONT ☐ PGP  
☐ Specification  
☒ Executed/Unexecuted Decl. - Fee \$ \_\_\_\_\_  
☐ Missing Parts/Missing Req.



☐ Preliminary Amendment \_\_\_\_\_ Pg's  
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☐ Amendment After Final  
☐ Notice of Appeal - Fee \$ \_\_\_\_\_

☐ Appeal Brief - Fee \$ \_\_\_\_\_  
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☐ Formal Drawings \_\_\_\_\_ Pg's

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☐ PTO-1499 Form \_\_\_\_\_ Pg's

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BMS-PG-5035

☒ Provisional Election of Species

RH/dms  
 Initials